REMARKS

Claim 7, 8, 10, 12, 14-18, 20, 22-32 are currently pending. As will be discussed in further detail below, claims 7, 20, 24, 25 and 31 have been amended to more distinctly claim that which Applicant regards as his invention. New claims 33-38 have been added to recite specific embodiments and are supported by the specification. Claims 8, 26-29 have been canceled without prejudice. Applicant reserves the right to file subsequent continuation and/or divisional applications on canceled subject matter.

1. **Claim Objections**

Claim 7, with dependent claims 10, 15-18, 20, 26, 27, 28, 30, 31, are objected to as reciting the non-elected subject matter of 5' and 3' non-coding regions and introns. It is requested that the recitation of 5' and 3' noncoding regions and "introns" be removed since they recited nonelected subject matter.

Applicants respectfully traverse the objection. The Restriction Requirement dated May 6, 2004 specifically recited that the election was a species election. It is stated on page 6 of said Restriction Requirement:

> Inventions V and VI contain claims directed to the following patentably distinct species of the claimed invention: an intron, a splice junction, a 5'-non-coding region, an expression control sequence, a transcription factor binding region and a 3'-non-coding region.
>
> Applicant is required under 35 USC 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 7, 9, 10 and 15-20 are generic.

Given that this is a species election, Applicants assert that it is not necessary to cancel "nonelected" subject matter.

2. **The Rejections Under 35 U.S.C. §103(a)**

Claims 7, 10, 15-20 and 24-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muzny et al, in view of Vogelstein et al. The Office Action states:

> With regard to the 103(a) rejection, Applicant argues that "First given that Muzny only discloses the sequence of the clone AC025423 but does not suggest that SEQ ID N0:4 or any other gene could be located on this clone and given that Vogelstein only provides a rough location for the MDM2 gene and the cDNA sequence which only constitutes a very small portion of the genomic sequence, one of ordinary skill in the art as of the priority date would not have had a reasonable expectation of success of obtaining the genomic sequence and subsequently the introns. At best as pointed out in the Office Action, there may have been a motivation to search the cDNA sequence against the entire genomic DNA in order to find the identical regions but not necessarily a reasonable expectation of success. However, that is not sufficient" (pages 8-9). This is not persuasive because the exact location of the gene is not necessary as long as its sequence is known as in the instant case. Further, Applicant does not explain why there is no expectation of success when finding non-coding regions using cDNA and genomic DNA was standard technique at the time of filing the current application.

Applicant respectfully traverses the rejection. First, Applicant notes that in order to more distinctly claim the subject matter of the invention, claims 7 and 24 have been amended to recite that the contiguous intron-exon and contiguous exon-intron region is located between nucleotides 41738-9502 of SEQ ID NO:4, wherein a fragment between nucleotides 41738-9502 of SEQ ID NO:4 encodes human mouse double minute 2 homolog depicted in SEQ ID NO:2. There was certainly no indication given in the cited art either singly or in combination regarding the location of the MDM2 gene encoding human mouse double minute 2 homolog depicted in SEQ ID NO:2 on AC025423. Thus the location of the MDM2 gene on AC025423 would not be obvious in view of the cited references. It would follow that the locations of contiguous exon-intron and intron-exon regions within the MDM2 gene would also not be obvious.

Furthermore, Applicant takes issue with the assertion made that given that finding non-coding regions using cDNA and genome DNA was standard technique at the time of filing the current application there would be a reasonable expectation of success. There is nothing stated in the Office Action as to how the state of the art teaches how given the teaching of a large genomic clone and the cDNA sequence of a particular gene, one of ordinary skill in the art could with particularity identify specific noncoding regions. There is no prior art that defines the complete genomic structure of a particular gene. This is necessary in order to accurately identify the claimed noncoding sequences in the instant invention. In this case, the teachings of the prior

art are limited to MDM2 cDNA sequences, knowledge of possible consensus sequences (but not their location in the MDM2 gene) and two possible locations of the MDM2 gene. One of ordinary skill in the art would have no idea as to the number of introns and the length of the 5' and 3' noncoding sequences in the MDM2 gene. It would have required undue experimentation to obtain such information. Thus one of ordinary skill in the art would not have a reasonable expectation of success of obtaining the claimed sequences.

Applicant respectfully points out that no one else did, in fact, find and isolate the genomic DNA, and no one else annotated the genomic DNA to define, among other things, introns, exons and sites of transcription factor binding sites. In fact, the present application reveals considerable information about the gene that was not known previously or even suspected. In retrospect, others might have made this invention, but they did not. The examiner is fundamentally objecting to the means by which the invention was made. This is not the correct standard to apply.

The Office Action further states

> As previously argued, there would not be any motivation to combine Muzny et al with Vogelstein et al. Muzny et al knew that clone AC025423 (from 1V11-61102) was from chromosome 12 but there is no evidence in the NCBI report of a sub-assignment to the p- or q-arm. Chromosome 12 is about 130 million base pairs long and is believed to contain several hundred genes (by analysis after 2001 and after the Applicant discovered the human MDM2 homologue gene). Further, there is no evidence that Muzny et al. knew whether the clone did or did not contain one or more genes and particularly whether it contained the gene encoded by SEQ ID NO:4. Vogelstein et al. placed the human MDM2 homologue gene at 12q12-14. Actually, this finding is incorrect. After the publication of Vogelstein, the gene was found not[sic] to be located at 12q12-14, whereas the gene is actually several millions of base pairs away at 12q15 (see Genecard attached hereto as Appendix B). There was actually a previous disclosure stating that the MDM2 was located between 12q14.3-15 (see, for example, Andersen et al., 1996, Mammalian Genome 7:780-783 and Bureau, 1995, Genomics 28: 109-112, submitted herewith as an IDS). However, given the conflicting locations published, one of ordinary skill in the art would not have known which location was actually correct. Clearly combining the disclosures of Muzny et al. with Vogelstein et al. would not have produced the claimed sequences, especially given Vogelstein's mistaken assignment of MDM2 to 12q12-14" (Remarks, pages 14-15). This is not

> persuasive because it is well known in the art that the localization on the chromosome is often imprecise. However, one of ordinary skill in the art would have been motivated to search the cDNA sequence against the entire genomic DNA in order to find the identical regions.

The Examiner's assertion that one of ordinary skill in the art would have expected that the location is often imprecise actually further supports Applicant's assertion that the claimed sequences were indeed nonobvious. If the location is imprecise, where would one of ordinary skill in the art know where to look? This is especially true with respect to the instant invention. In Applicant's view, undue experimentation would have been involved. A reference is not applicable as prior art if it cannot enable one to produce the claimed product without undue experimentation. *Elan Pharm., Inc. V. Mayo Found. For. Med. Educ. & Research*, 346 F.3d 1051, 68 USPQ2d 1373 (Fed. Cir. 2003). Further, in view of the prior art disclosures, the location of the MDM2 gene discovered by the Applicant was unexpected. Objective evidence such as commercial success, failure of others, long-felt need, and unexpected results must be considered before a conclusion on obviousness is reached. *Minnesota Mining and Manufacturing Co., v. Johnson & Johnson Orthopaedics Inc.*, 976 F.2d 1559, 24 USPQ2d 13221 (Fed. Cir. 1992).

Applicant, as argued in the previous response submitted, asserts that at best the combined teachings of Muzny and Vogelstein would constitute "obvious to try". It is well established case law that the "obvious to try" standard is not the standard under 35 USC §103. *In re O'Farrell* 853 F.2d 894 (Fed. Cir. 1988). *In re O'Farrell* provides two "obvious to try" situations:

> In some cases, what would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.....
>
> In others, what was "obvious to try" was to explore a new technology or general approach that seem to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

In Applicant's view, both situations apply. Even if one of ordinary skill in the art used probes containing splice junction consensus sequences to identify such sequences present on the Muzny sequence, at best one of ordinary skill in the art would not know whether it belonged to

the MDM2 gene or some other gene present on this sequence. No direction was given as to where in AC025423 the MDM2 gene is located and further where splice junctions would be located. Even if prospective splice sites are located, one of ordinary skill in the art would not have any idea as to whether they are correct.

It should be noted that annotation of the human genomic DNA was still relatively new as of the priority date of the instant application. Even assuming *arguendo* that finding noncoding regions using cDNA and genomic DNA was standard technique, the means to make the invention does not predict the claimed invention. Specifically the means used to make the invention do not predict the claimed nucleic acid molecules. BLASTN, TBLASTN, etc. do not themselves predict gene-specific results It is Applicant's view that only general guidance is provided. This is not sufficient.

The Office Action further asserts

> Applicant further argues "First, there are a large number of sequences to choose from, the sequences contained within AC025423; the permutations and combinations are indeed significant given that the cDNA only constitutes such a minute portion (1.6%) of the AC025423 sequence" (page 10, lines 1-3). This is not persuasive because Applicants does not explain why the fact that cDNA constitutes 1.6% of the AC025423 sequence prevents finding non-coding regions in the genomic DNA. Applicants further argues relating to the Bell court "Analogously, the prior art discloses the known MDM2 cDNA and there are large numbers of possibilities as to which sequences may be the genomic sequence but no suggestion as to which possibility is indeed the genomic sequence" (page 10). This is not persuasive because Applicant does not give any example when indeed he was faced with multiple choices in identifying any non-coding region. unless said sequence is very small, it is not clear why there is a large number of sequences and not a single one.

Applicant, in response, takes issue with the assertion made above that "unless said sequence is very small, it is not clear where there is a large number of sequences". This is merely speculative on the Examiner's part. Further, it is Applicant's view that given that the cDNA constitutes just 1.6% of the AC025423 sequence is in itself evidence of the unpredictablilty of determining the entire sequence of the MDM2 gene and thus contiguous intron-exon and exon-intron regions. The Examiner is in effect asserting that just because Applicant did isolate the claimed nucleic acid molecule, it must have been obvious to do so. It is

well established case law that the fact that the inventors were ultimately successful is irrelevant to whether one of ordinary skill in the at the time the invention was made would have reasonably expected success. *Life Technologies, Inc. v. Clontech Laboratories Inc., 56 USPQ2d 1186, 224 F.32 1320 (Fed. Cir. 2000).* The assertions made in the Office Action represents the impermissible use of hindsight. *In re Kotzab*, 217 F.32 1365, 55 USPQ2d 1313.

In view of the above arguments and the amendments of claims 7 and 24, Applicant asserts that the rejections under 35 USC 103 have been overcome. Therefore, Applicant respectfully requests that the rejection be with withdrawn.

7. Conclusion

In view of the foregoing, Applicants assert that the claims are now in condition for allowance. Early action to that end is respectfully requested. The Examiner is invited to contact the undersigned at (914) 712-0093 if she has any questions.

Respectfully submitted,

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